Daytime measurements underestimate nocturnal oxygen desaturations in pulmonary arterial and chronic thromboembolic pulmonary hypertension

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Abstract: Background: Nocturnal hypoxemia is important in precapillary pulmonary hypertension (pPH) as it worsens pulmonary hemodynamics. Whether daytime oxygen saturation (SpO(2)) predicts nocturnal hypoxemia in pPH patients has not been conclusively studied. Objectives: To investigate the prevalence of nocturnal hypoxemia in comparison to daytime SpO(2) and disease severity in ambulatory patients with pulmonary hypertension. Methods: Consecutive patients diagnosed with pPH classified as either pulmonary arterial (PAH) or chronic thromboembolic pPH (CTEPH) had daytime resting and exercise SpO(2) (at the end of a 6-min walk test); thereafter, they underwent overnight pulse oximetry at home. Functional class, pro-brain natriuretic peptide (pro-BNP) and the tricuspid pressure gradient were assessed. Results: Sixty-three patients [median (quartiles) age 62 (53; 71), 43 females] with PAH (n = 44) and CTEPH (n = 19) were included. The resting SpO(2), exercise SpO(2), and mean nocturnal SpO(2) were 95% (92; 96), 88% (81; 95), and 89% (85; 92), respectively. Forty-nine patients (77%) spent >10% of the night with SpO(2) <90% (desaturators), and 33 (52%) spent >50% of the night with SpO(2) <90% (sustained desaturators). The positive predictive values of daytime SpO(2) >90% for being a nocturnal nondesaturator or sustained nondesaturator were 25 and 53%, respectively. Nocturnal SpO(2) was negatively correlated with the tricuspid pressure gradient, but not with functional class, 6-min walk test, or pro-BNP. Conclusions: Nocturnal hypoxemia is very common in PAH and CTEPH despite often normal daytime SpO(2) and reflects disease severity. Nocturnal pulse oximetry should be considered in the routine evaluation of pPH patients and research should be directed toward the treatment of nocturnal desaturation in pPH.

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Daytime Measurements Underestimate Nocturnal Oxygen Desaturations in Pulmonary Arterial and Chronic Thromboembolic Pulmonary Hypertension

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Key Words
Chronic thromboembolic pulmonary hypertension · Pulmonary arterial hypertension · Sleep disordered breathing

Abstract
Background: Nocturnal hypoxemia is important in precapillary pulmonary hypertension (pPH) as it worsens pulmonary hemodynamics. Whether daytime oxygen saturation (Spo_2) predicts nocturnal hypoxemia in pPH patients has not been conclusively studied. ***Objectives:*** To investigate the prevalence of nocturnal hypoxemia in comparison to daytime Spo_2 and disease severity in ambulatory patients with pulmonary hypertension. ***Methods:*** Consecutive patients diagnosed with pPH classified as either pulmonary arterial (PAH) or chronic thromboembolic pPH (CTEPH) had daytime resting and exercise Spo_2 (at the end of a 6-min walk test); thereafter, they underwent overnight pulse oximetry at home. Functional class, pro-brain natriuretic peptide (pro-BNP) and the tricuspid pressure gradient were assessed. ***Results:*** Sixty-three patients [median (quartiles) age 62 (53; 71), 43 females] with PAH (n = 44) and CTEPH (n = 19) were included. The resting Spo_2, exercise Spo_2, and mean nocturnal Spo_2 were 95% (92; 96), 88% (81; 95), and 89% (85; 92), respectively. Forty-nine patients (77%) spent >10% of the night with Spo_2 <90% (desaturators), and 33 (52%) spent >50% of the night with Spo_2 <90% (sustained desaturators). The positive predictive values of daytime Spo_2 >90% for being a nocturnal nondesaturator or sustained nondesaturator were 25 and 53%, respectively. Nocturnal Spo_2 was negatively correlated with the tricuspid pressure gradient, but not with functional class, 6-min walk test, or pro-BNP. ***Conclusions:*** Nocturnal hypoxemia is very common in PAH and CTEPH despite often normal daytime Spo_2 and reflects disease severity. Nocturnal pulse oximetry should be considered in the routine evaluation of pPH patients and research should be directed toward the treatment of nocturnal desaturation in pPH.

Introduction

Precapillary pulmonary hypertension (pPH) is defined as a resting mean pulmonary artery pressure ≥25 mm Hg along with a pulmonary capillary wedge pressure ≤15 mm Hg. In the absence of relevant lung diseases, the two major groups are pulmonary arterial hypertension (PAH), including idiopathic and associated forms,

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and chronic thromboembolic pulmonary hypertension (CTEPH) [1, 2]. Despite major advances in therapy over the last two decades, pPH remains a progressive and incurable condition with the exception of those CTEPH patients who are eligible for surgery [3–6]. Sleep reduces respiratory drive and airway stability and may therefore lead to alveolar hypoventilation and ventilatory instability with apnea/hypopnea associated with intermittent or sustained hypoxemia. Previous studies have shown that nocturnal hypoxemia is common in patients with PAH, with more than two thirds of patients affected [7, 8]. Hypoxia induces pulmonary vasoconstriction via its effects on pulmonary vascular smooth muscle and endothelial cells and therefore may lead to elevated pulmonary artery pressure [9]. This effect has been shown even in transient hypoxia [10]. Improved functional capacity and survival have been demonstrated with long-term oxygen therapy in hypoxemic patients with chronic obstructive pulmonary disease (COPD) [11, 12]. Supplemental oxygen can improve elevated pulmonary arterial pressure in mild pPH [13, 14]. Previous studies have shown that over a third of patients with right heart failure due to pPH suffer from Cheyne-Stokes respiration/central sleep apnea [15, 16], similar to patients with left ventricular heart failure. In left heart failure, noninvasive positive pressure ventilation or oxygen might be effective therapies as adjuncts to drug treatment [17]; however, studies in pPH are lacking. Other reasons for reduced nocturnal oxygen saturation (Sp_{O_2}) might be an increased ventilation perfusion mismatch and impairment of respiratory muscle efficiency due to the recumbent position.

In order to better define the role of nocturnal hypoxemia in pPH not associated with lung diseases, we performed nocturnal pulse oximetry in a cohort of outpatients with PAH or CTEPH in their homes and compared the results to daytime office measurements at rest and during exercise, and to pulmonary hemodynamics and functional status. We hypothesized that low nocturnal Sp_{O_2} would be associated with impaired hemodynamics and poor functional status and that daytime Sp_{O_2} would not reliably predict nocturnal desaturation.

Methods

Patients

Consecutive patients diagnosed with PAH or CTEPH at our tertiary care outpatient clinic who were not using supplemental oxygen were eligible for enrolment upon written informed consent from 2007 to March 2011. The study was approved by the local ethical review board. All patients were diagnosed according to current guidelines and had undergone right heart catheterization at the time of the initial evaluation. At the time of this study, they were in stable condition and had been on the same therapy for at least 1 month.

Assessments

Weight and height were measured and the WHO functional class was assessed. The tricuspid pressure gradient was assessed by echocardiography [18]. After a rest period of ≥10 min in a comfortable sitting position, patients underwent measurements of blood pressure, pulse rate, and resting Sp_{O_2} by pulse oximetry using a finger probe (Pulsox-300i; Anandic Medical Systems, Switzerland). Patients subsequently performed a 6-min walk test (6MWT) according to standard guidelines and Sp_{O_2} was monitored continuously. The lowest Sp_{O_2} during the 6MWT was noted as the exercise Sp_{O_2} [19]. N-terminal pro-brain natriuretic peptide (NT-pro-BNP) was measured in a venous blood sample.

Ambulatory nocturnal pulse oximetry was performed by fitting a finger probe and an oximeter to the patient's wrist (Pulsoxi-300i; Anandic Medical Systems, or Vivo Metrics, Ventura, Calif., USA) and giving thorough instructions to wear it overnight at home. Patients were advised to mark their lights-off time in the evening and lights-on time in the morning and any specific events during the night in a symptom log. Patients returned the pulse oximeter the next day and data were downloaded for analysis. The first 32 patients had additional ambulatory respiratory polygraphy (LifeShirt, Vivo Metrics) as previously described [15, 20].

Data Analysis and Statistics

Desaturation during the 6MWT was defined as a decrease in Sp_{O_2} ≥4% and below 90%. Nocturnal pulse oximetry was analyzed from lights-off to lights-on as time in bed (TIB). The mean nocturnal Sp_{O_2} and the percent of TIB spent with Sp_{O_2} <90% were derived. Patients who had spent >10% of the TIB with Sp_{O_2} <90% were classified as desaturators. Among these, patients who had spent >50% of the TIB with Sp_{O_2} <90% were classified as sustained desaturators. The oxygen desaturation index was computed as the number of desaturations ≥4%/h. Ambulatory cardiorespiratory sleep studies were obtained in a subset of patients and analyzed as previously described [15]. Data are presented as medians (quartiles) and were compared using the Mann-Whitney U test, the Kruskal-Wallis test, and Fisher's exact test. Pearson's correlation and logistic regression were used to evaluate associations between continuous variables. Statistical tests were two-tailed and $p < 0.05$ was considered statistically significant.

Results

Patients

Sixty-three pPH patients were included in the study (table 1). Slightly more than half of the patients suffered from idiopathic PAH, a third from CTEPH, and the remainder from other associated PAH [1]. Patients were in WHO functional classes II–IV and had a moderately reduced 6MWT and a markedly increased tricuspid pres-

sure gradient. Patients were on endothelin receptor antagonists (n = 41), phosphodiesterase-5 inhibitors (n = 35), and prostanoids (n = 14) according to current guidelines [18].

Pulse Oximetry Data and Sleep Studies

Results of the daytime and nocturnal oximetries of all patients and the additional home respiratory polygraphy in 32 patients are shown in table 2. In our cohort of patients who were not using supplemental oxygen, the median daytime resting SpO_2 was in the normal range [95 (92; 96)], with only 8 patients having a resting $SpO_2 \leq 90\%$. The exercise SpO_2 was significantly lower and over half of patients desaturated by $\geq 4\%$ to values $<90\%$.

Nocturnal pulse oximetry revealed a median SpO_2 during TIB of 89% (85; 92), with 49 of 63 patients (78%) spending >10% of the time with an $SpO_2 < 90\%$ (desaturators). Thirty-three of these (52% of the entire cohort) spent >50% of the TIB with $SpO_2 < 90\%$ (sustained desaturators). The severity distribution of nocturnal desaturators is shown in figure 1. We found no difference in patients' characteristics or daytime or nocturnal SpO_2 between PAH and CTEPH.

Association between Daytime and Nocturnal Assessments

Baseline characteristics of nocturnal nondesaturators, desaturators, and sustained desaturators are shown in table 3. Desaturators had significantly higher tricuspid pressure gradients and a significantly lower exercise SpO_2 along with greater exercise desaturation compared to nondesaturators, and the proportion of patients with sleep apnea (defined as an apnea/hypopnea index ≥ 10/h or ≥ 10/h oxygen desaturations) was also higher among desaturators.

We found significant correlations between the daytime resting and exercise SpO_2 and the mean nocturnal SpO_2 ($r = 0.491$ and $r = 0.452$, $p < 0.001$ in both instances; fig. 2a, b). The tricuspid pressure gradient correlated negatively with the mean nocturnal SpO_2 and positively with the time spent with an $SpO_2 < 90\%$ ($r = -0.349$ and $r = 0.346$, $p = 0.007$ and $p = 0.008$; fig. 3a, b). Multiple regression analysis with the nocturnal SpO_2 as the dependent factor and age, BMI, 6MWT, pro-BNP, tricuspid pressure gradient, and resting and exercise SpO_2 as independent factors revealed that only daytime resting SpO_2 and the tricuspid pressure gradient were independently correlated with the mean nocturnal SpO_2 [$p = 0.018$ and $p = 0.003$, standardized coefficient B (95% CI) 0.321 (0.073–0.744) and –0.403 (–0.112 to 0.025)]. We did not find a signifi-

Table 1. Patient characteristics

	n (%) or medians (IQR)
Total patients	63 (100)
Females	43 (68)
Age, years	62 (53; 71)
pPH classification	
Idiopathic PAH	34 (54)
Associated PAH	10 (16)
Chronic thromboembolic pPH	19 (30)
WHO functional class	
II	24 (38)
III	31 (49)
IV	8 (13)
BMI	26 (23; 29)
Mean pulmonary arterial pressure[a], mm Hg	41 (30; 51)
Pulmonary vascular resistance[a], dyn·s·m^{-5}	571 (331; 793)
Cardiac index[a], l/min/m^2	2.6 (2.3; 3)
Mixed venous oxygen saturation[a], %	64 (58; 68)
Tricuspid pressure gradient, mm Hg	60 (43; 80)
NT-pro-BNP (normal <130), ng/l	718 (221; 1,510)
6-min walking distance, m	455 (359; 534)

[a] Invasive hemodynamics obtained at the baseline diagnostic right heart catheterization.

Table 2. Daytime and ambulatory overnight pulse oximetry and sleep studies

	n (%) or medians (IQR)
Ambulatory resting SpO_2, %	95 (92; 96)
Daytime resting $SpO_2 \geq 91\%$	55 (87)
Exercise SpO_2 (end of 6MWT), %	88 (81; 95)
Median desaturation during exercise	–5 (–11; –1)
Exercise desaturators (≥4% and absolute <90%)	33 (53)
Mean nocturnal SpO_2, %	89 (85; 92)
Time spent with $SpO_2 < 90\%$, % TIB	51 (13; 84)
>10% TIB with $SpO_2 < 90\%$	49 (78)
>50% TIB with $SpO_2 < 90\%$	33 (52)
ODI (≥4%), events/h	3 (1; 7)
ODI ≥10/h	10 (16)
AHI[a], events/h	10 (6; 19)
AHI ≥10 events/h[a]	16 (50)
PB[a], % TIB	9 (4; 13)
PB ≥10% TIB[a]	15 (47)

ODI = Oxygen desaturation index; AHI = apnea/hypopnea index; PB = periodic breathing.

[a] Thirty-two patients with simultaneous ambulatory cardiorespiratory sleep study.

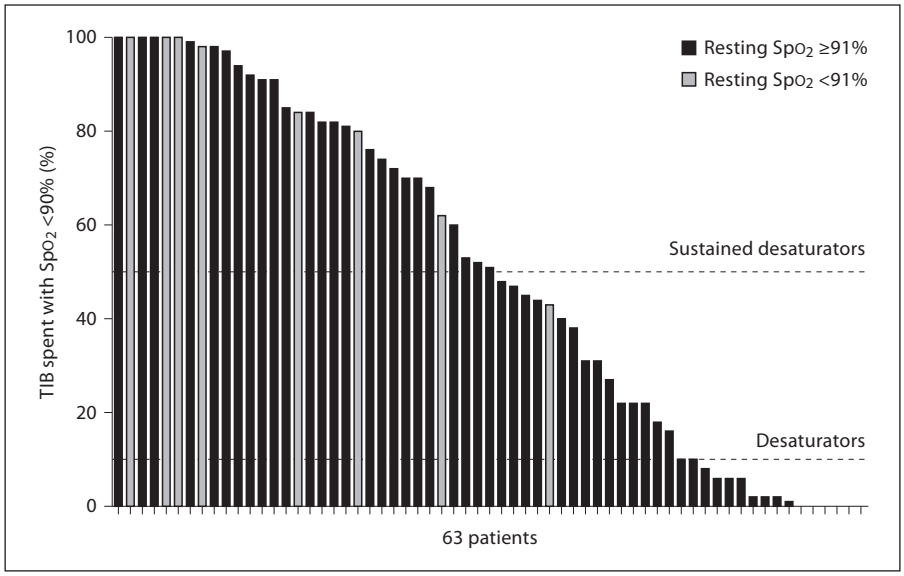

Fig. 1. The percentage of TIB spent with an Sp_{O_2} <90% is shown as a bar for every single pPH patient.

Table 3. Differential characteristics of nocturnal nondesaturators, desaturators, and sustained desaturators

	Nondesaturators	Desaturators	Sustained desaturators
Total patients	14 (22)	49 (76)	33 (52)
Females	9 (56)	34 (71)	21 (66)
Age, years	65 (40; 72)	61 (53; 71)	61 (54; 71)
pPH classification			
Idiopathic PAH	8 (53)	26 (54)	23 (72)
Associated PAH	3 (20)	7 (14)	0
Chronic thromboembolic pPH	4 (26)	15 (31)	19 (28)
WHO functional class			
II	6 (43)	18 (37)	12 (38)
III	8 (57)	23 (47)	17 (53)
IV	0 (7)	8 (16)	4 (12)
BMI	28 (26; 29)	26 (22; 29)	26 (23; 28)
Tricuspid pressure gradient, mm Hg	43 (38; 55)	66 (66; 50; 83)*	75 (58; 89)#, ‡
NT-pro-BNP (<130), ng/l	563 (240; 1,716)	718 (206; 1,371)	1,048 (206; 1,689)
6MWT, m	529 (385; 568)	450 (363; 506)	450 (367; 516)
Daytime resting Sp_{O_2}, %	96 (95; 97)	94 (92; 96)	93 (91; 96)#
Exercise Sp_{O_2} (end of 6MWT), %	95 (89; 97)	87 (80; 91)**	86 (78; 91)#, ‡
Mean desaturation during exercise, %	–2 (–7; 0)	–6 (–11; –2)*	–6 (–15; –2)
Exercise desaturators (≥4% and absolute <90%)	5 (33)	28 (58)	19 (59)
Mean nocturnal Sp_{O_2}, %	94 (93; 95)	88 (85; 90)**	86 (84; 88)##, ‡
ODI, events/h	2 (1; 4)	3 (1; 9)	3 (1; 9)
ODI >10 events/h	0	10 (21)*	6 (20)
AHI, events/h[a]	9 (5; 18)	10 (6; 19)	10 (6; 19)
AHI >10 events/h[a]	3 (38)	13 (54)	8 (50)
PB, % TIB[a]	5 (4; 9)	11 (4; 13)	12 (5; 15)
PB ≥10 % of TIB[a]	3 (38)	12 (50)	9 (56)

Values are numbers (%) or medians (IQR) unless otherwise stated. AHI = Apnea/hypopnea index; PB = periodic breathing; ODI = oxygen desaturation index. * $p < 0.05$ and ** $p < 0.001$ for desaturators vs. nondesaturators. # $p < 0.05$ and ## $p < 0.001$ for sustained desaturators vs. nonsustained desaturators (patients who spent less than 50% of their nighttime with an Sp_{O_2} <90%). ‡ $p < 0.05$ for between-group differences by analysis of variance for spending <10, 10–49, and ≥50% of the night with an Sp_{O_2} ≤90%.

[a] Thirty-two patients with simultaneous ambulatory cardiorespiratory sleep study.

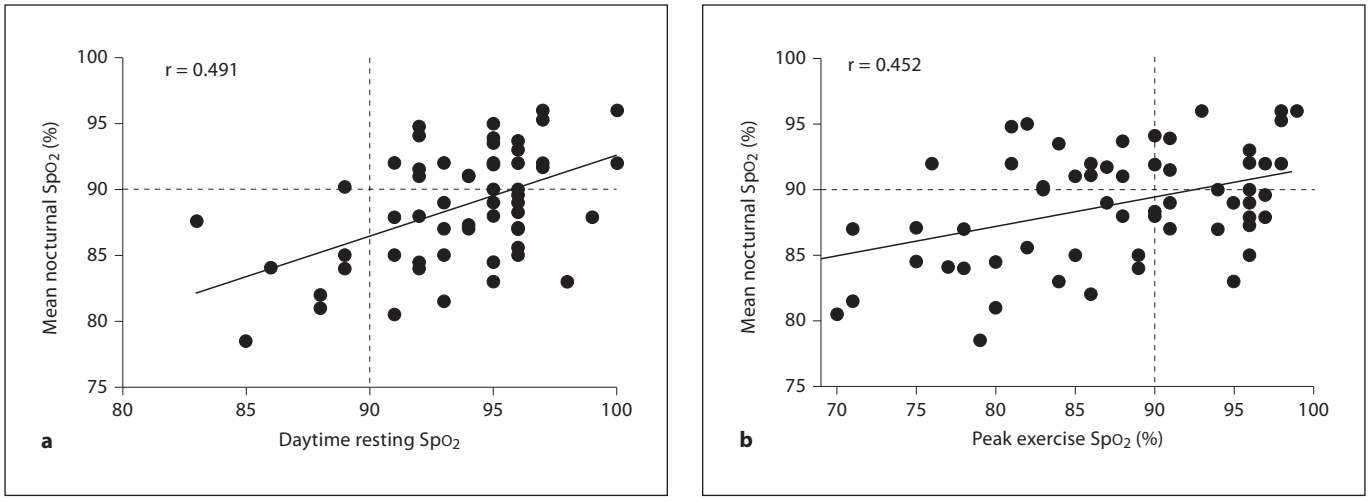

Fig. 2. The correlations between the mean nocturnal SpO_2 and the daytime resting SpO_2 (**a**) and exercise SpO_2 at the end of a 6MWT (**b**) are shown. The correlations for both daytime assessments are relatively weak and nocturnal desaturation is found despite normal daytime SpO_2 measures in the majority of patients.

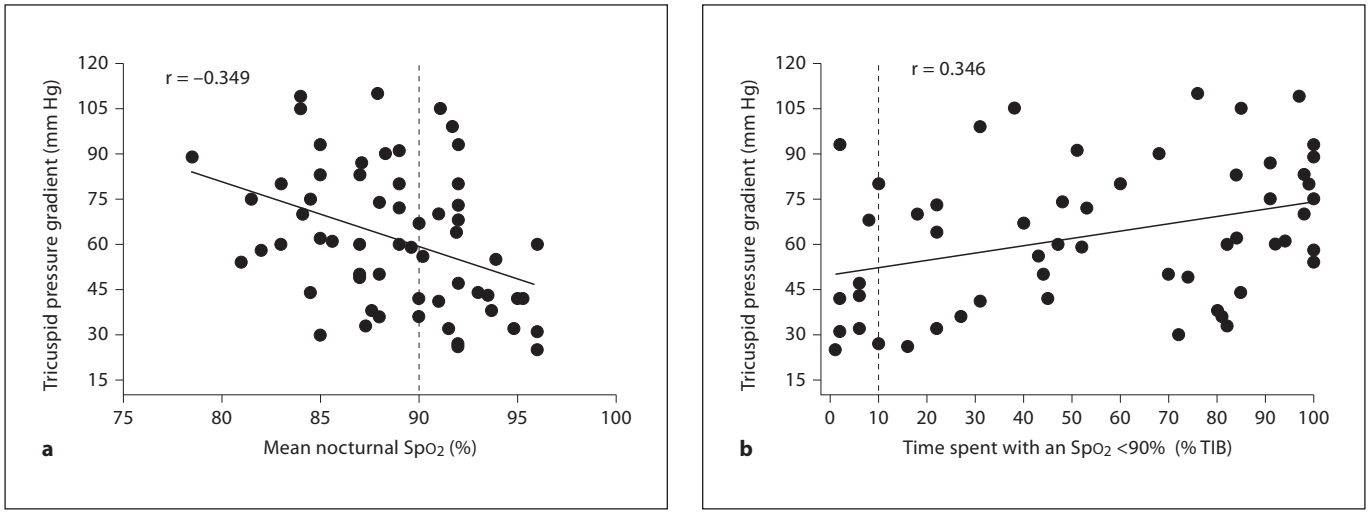

Fig. 3. The correlations between the mean nocturnal SpO_2 and the tricuspid pressure gradient (**a**) and time spent with an SpO_2 <90% and the tricuspid pressure gradient (**b**) are shown.

cant correlation of age, WHO class, 6MWT, or pro-BNP with nocturnal desaturation.

The positive predictive value of a daytime resting SpO_2 ≥91% to predict patients who would not be nocturnal desaturators was only 25%, corresponding to a very low sensitivity (16%; only 8 out of 49 patients with daytime SpO_2 ≥91% would not desaturate during TIB). For patients who did not desaturate during exercise, their risk of being a nocturnal desaturator was still 83%.

Discussion

In the present study of patients diagnosed with PAH and CTEPH, we found that daytime SpO_2 measurements do not reliably predict nocturnal SpO_2. Half of the patients spent more than half of their nighttime with an SpO_2 <90%, and only a minority of the patients (25%) with a daytime resting SpO_2 >90% do not desaturate during TIB. Nocturnal desaturation was significantly and

independently correlated with the transtricuspid pressure gradient, even when corrected for age, gender, daytime SpO_2, NT-pro-BNP, and the 6MWT. These study results are important as they suggest that many pPH patients have nocturnal hypoxemia, a treatable condition associated with hemodynamic impairment in pPH.

Sleep poses profound physiological alterations to the respiratory system even in healthy subjects, which may lead to oxygen desaturation [21]. Possible underlying mechanisms include alterations in ventilation-perfusion [22], a reduced functional residual capacity due to a recumbent position, and reduced respiratory drive with relative alveolar hypoventilation [8, 23]. In patients with preexisting lung or heart disease, these mechanisms may interact and promote sleep-related breathing disturbances. Oxygen deprivation in pulmonary vascular cells leads to vasoconstriction and consecutive elevation of the pulmonary vascular resistance [9, 24–26]. This mechanism might be deleterious in patients with preexisting pPH by augmenting the disease progression and pulmonary vascular remodeling [26]. Therefore, many guidelines recommend that patients with preexisting chronic lung diseases be treated with supplemental oxygen if the daytime resting partial pressure of oxygen is $\leq$8 kPa [27, 28]. Although oxygen administration acutely reduces pulmonary vascular resistance in certain patients with PAH and CTEPH, data about the effect of long-term oxygen therapy in pPH not associated with lung diseases is not available. In the absence of data from randomized controlled trials, current pPH guidelines base their recommendations for supplemental oxygen in PAH and CTEPH on old data available from cohorts of patients with pPH associated with chronic obstructive lung disease [2, 18, 29]. Data on the prevalence, circadian occurrence, and clinical correlates of hypoxemia in patients suffering from PAH and CTEPH are therefore highly warranted.

In our pPH collective we found a high prevalence of nocturnal desaturators, with more than three fourths of pPH patients spending >10% of their nighttime with an SpO_2 <90%. Over 50% of patients even spent more than half of their night with a low SpO_2 (sustained desaturators). These findings corroborate findings in smaller cohorts including patients with idiopathic PAH, where 70 and 77%, respectively, were found to spend >10% of night with an SpO_2 <90% [7, 8]. Sustained nocturnal desaturators were slightly less present in the cohort of Minai et al. [8] (37%) compared to the current study (52%), although both populations had a comparable hemodynamic profile. The reason for this difference is not clear. In our study nocturnal oxygen pulse oximetry was performed in the patients' homes. The setting of pulse oximetry in the cohort of Minai et al. [8] is not mentioned and it is not clear if their PAH cohort was allowed to use supplemental oxygen during nights as they were during the 6MWT. In addition, one third of the patients in our cohort had CTEPH. However, we found similar characteristics, oxygen profiles, and proportions of nocturnal desaturators in PAH and CTEPH. We can therefore extend the strikingly high percentage of nocturnal desaturators and sustained desaturators to patients diagnosed with CTEPH.

Our pPH patients with nocturnal desaturation were not using supplemental oxygen. The majority had normal values of daytime resting SpO_2 $\geq$91% (55/63 patients; fig. 1). Despite the preserved resting SpO_2 $\geq$91%, the majority (75%) had moderate-to-severe nocturnal hypoxemia, i.e. they were desaturators or sustained desaturators. A daytime resting SpO_2 $\geq$91% therefore had a very low positive predictive value for detecting nocturnal nondesaturators (25%), and the diagnostic performance of daytime resting SpO_2 in predicting nocturnal desaturators was poor. Nocturnal hypoxemia may well be important in pPH as it may worsen pulmonary hemodynamics. However, the significance of oxygen desaturation during sleep in pPH and other chronic lung diseases is not well studied. Sleep research in this field mainly focused on associated sleep apnea [15, 30]; however, nocturnal oxygen desaturation might be found even without significant sleep apnea [8, 31]. In this study half of the patients underwent simultaneous ambulatory cardiorespiratory sleep study. As might be expected, we found slightly more patients with sleep apnea among nocturnal desaturators; however, the difference was not significant. Almost half of the nocturnal desaturators did not fulfill the criteria for sleep apnea or periodic breathing. In this regard our data coincided with other reports describing markedly reduced nocturnal SpO_2 in patients with preexisting lung diseases without sleep apnea [8, 30]. Furthermore, the herein reported mean nocturnal SpO_2 during sleep might even underestimate the real oxygen desaturation during sleep, as we did not include electroencephalogram for sleep staging and we can therefore not exclude that during some investigated periods patients were awake in bed. Whether oxygen therapy would have any impact on performance, disease progression, and quality of life in nocturnal desaturators with pPH is not known to date. Various national and international guidelines recommend prescribing supplemental oxygen in patients with preexisting lung disease if a daytime resting oxygen partial pressure (PaO_2) $\leq$8 kPa ($\leq$60 mm Hg) and right heart strain are present [28, 32, 33]. These recommendations

are mainly based on data available from a cohort of patients with COPD. For other chronic lung diseases such as parenchymal lung diseases, cystic fibrosis, or pPH the evidence for long-term oxygen therapy is even more limited and data on supplemental oxygen for those who desaturate only during exercise and/or sleep are scarce. Supplemental oxygen has been shown to increase exercise capacity in parenchymal lung disease and cystic fibrosis [34, 35]; data on pPH and nocturnal oxygen therapy is not available. Controlled studies in this field are imperative, as overuse of supplemental oxygen might also be harmful as has been recently described for acute exacerbations of COPD [36].

We found a strong negative correlation of nocturnal desaturation with the tricuspid pressure gradient. This strong correlation persisted in multivariate models correcting for age, exercise capacity, and resting SpO_2. Therefore, the risk of being a nocturnal desaturator increases with hemodynamic disease severity. It may well be that pulmonary hemodynamics and nocturnal hypoxemia have a vicious mutually reinforcing relation.

In summary, we found in the hitherto largest pPH collective including PAH and CTEPH that nocturnal oxygen desaturation is highly prevalent, underestimated by daytime assessments and independently associated with hemodynamic disease severity. Therefore, we suggest that nocturnal pulse oximetry be included in the diagnostic pPH algorithm and that the potential benefit of supplemental oxygen in nocturnal desaturator be evaluated in future studies.

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Financial Disclosure and Conflicts of Interest

None of the authors has any conflict of interest to report.

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